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10/069,215	03/19/2002	Stephen Thom	06275-244001	1818

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EXAMINER	
PATEL, SUDHAKER B	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,215	THOM ET AL.	
	Examiner	Art Unit	
	Sudhaker B. Patel, D.Sc.Tech.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' communication paper #10 dated 9/22/03 is acknowledged.

Election/Restrictions

Because applicants did not distinctly and specifically point out the supposed errors in the restriction/election requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Applicant's election without traverse of invention of Group II, and also election of species of Example 365 as recited in page 92 (= N- (1-benzyl-4-piperidinyl)-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl] propanamide).

Applicants are reminded of the election of species guidelines provided in MPEP 803.02, which are followed for the examination.

The elected species of compound of Example 365 as stated earlier has following meanings for variables in the generic Formula (I) of claim 1:

X1, X2, X3, X4 and Z	= -CH2- i.e. piperidine N-CH2- core;
R6	= Optionally substituted phenyl-;
R1	= 1,2,4-oxadiazole substituted by a pyridine ring at 3-position; 3-14 membered saturated or unsaturated ring system which consists of upto 4-rin g heteroatoms independently selected from O.N.S, and the ring is optionally substituted;
m,n	= zero;
T	= -CO-NH-.

Initial search with above definitions of the R1, no prior art was found. Therefore, search was expanded to R1 = other heterocycle optionally substituted, and prior art(s) were found(See rejections bellow). As per rules stated earlier the examination of this application limited to all other than stated above meanings of the variables i.e. R definition does not include phenyl; T does not include NR10, NR11CONR1o or CONR10R11; Z does not include CO, CR4R5-Z1.

Since claims 1-11 link with other inventions, they will be examined bearing in mind the subject matter and species as elected by applicants and restriction as stated above. 37 CFR 1.142(b. Election was made without traverse in Paper # 10.

Restriction/election is considered proper and is now made FINAL.

First action on merits follows.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 1/22/03 as paper # 8 is being considered by the examiner. Signed copy of PTO Form 1449 is enclosed with this communication for applicants' record.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim1-8, rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A). Claim 1 recites R1 group for a compound as:" optionally comprises up to 2 ring carbon atoms that form CO groups and which optionally further comprises up to 4 ring heteroatoms". Deletion of "comprises" and correction to "consisting of" is required.

(B). Claim 1 recites R1, R6 and other variables (where applicable) as:" heterocyclyl, heterocyclllyloxy", the claim does not exactly state nature of heterocycle, ring size, number of heteroatoms in a ring, exact arrangement of the heteroring, and exact point of attachment to the carbon atom of the main core.

(C). Claim 1 recites:"The present invention provides a compound of Formula(I)". Correction to:" A compound of Formula(I)" is required.

(D). Claim 1 recites on the compound of Formula (I). Correction to:" A compound of Formula(I), or pharmaceutically acceptable salt or solvate thereof" is required.

Claim Rejections - 35 USC § 101

4. Claims 9,10 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a step or process for using a compound for manufacture of a medicament and use of the same or a compound of Formula (I) in therapy respectively or asserted utility or a well established utility.

The claims are related to process of making a medicament and process of using the compound in therapy. Claims do not state definitely the exact process or steps involved in making, and the exact process of administration as well as the nature of therapy.

Claims are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a process or steps asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for asthma, does not reasonably provide enablement for treating inflammatory disease generically. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

7. Specification in page 1 defines inflammatory diseases and disorders as allergic as well as autoimmune pathologies. These diseases involve chemokines having C-X-C and C-C structures which are different. And general. This is not a single and specific disease.
8. In cases directed to chemical compounds which are being used for their physiological/biological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See in re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group and In re Wiggins 179 USPQ 421.
9. " Compounds, their pharmaceutically acceptable salt(s), solvate, and their pharmaceutical composition(s)" as recited in the claims read on all such moieties regardless of complexity of structure and point of attachment to the aliphatic or carboxylic or aromatic or heterocyclic core or bridge/chain for which there is no sufficient teaching how to make and how to use at any one selective location among the many possible sites present. The situation is more confusing when a skilled person in the art tries to visualize the multiple possibilities of combining a compound of claim 1(or claims dependent on it) and/ or its pharmaceutical composition for treating a patient having diseases or conditions associated with inflammation in general. Applicants provide no reasonable assurance that any and all derivatives of the instant compounds and their compositions as outlined, will have ability to generate the compounds in vivo or in vitro by one or more processes.

10. In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:***(I).*** The nature of invention;***(2).*** the state of prior art ;***(3).*** the predictability or lack thereof in the art; ***(4).*** the amount of direction or guidance present;***(5).*** the presence or absence of working examples;***(6).*** the breadth of the claims, and ***(7).*** the quantity of experimentation needed.

The claims are drawn to compounds, compositions, and method(s) (but not limited to) of treating a patient having diseases or conditions associated with inflammation in general.

1). The nature of the invention: The compounds and their method of use claim(s) are drawn in part to use them for treating a patient suffering from diseases or conditions associated with inflammation in general.

2). The state of prior art: There are no known compounds of similar structure (i.e. compounds of invention of Group (II) which have been demonstrated for the treatment of infection or disease as recited here in a generic way.

3). The predictability or lack thereof in the art: It is presumed in the use for patient(s) who are humans or animals suffering from infection or disease related to activity of chemokine receptor as claimed herein, there is a way of identifying those patient(s) who

may develop any kind of physiological conditions including (but not limited to) a single disease. There is no evidence of record, which would enable the skilled artisan in the identification of the patient(s) who have the potential of becoming afflicted with the physiological conditions related to inflammation, and diseases yet to be discovered, and as claimed herein.

4). The amount of direction or guidance present and 5).: The presence or absence of working examples: There are no doses present to direct one to treat a potential host from an infection or disease, and other multiples of physiologically related condition(s) of various types.

6). The breadth of the claims: The claims are drawn to physiological conditions (not limited to) for treatment of inflammation or disease related to chemokine receptor activity which are not related and whose treatment(s) is unknown by a compound of instant invention.

7). The quantity of experimentation need would be and undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

11. ***Discussion about inflammatory diseases and conditions:***

Enablement for the scope of "inflammatory diseases" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together,

typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulites is inflammation of the tissues around eye, and Orbital cellulites is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

12. ***Following references are cited to show the state of art related to inflammation:***

Mechanism of diseases formed by inflammation:

- Granata et al (PubMed Abstract 12876405, also cited as Int. Arch. Allergy Immunolo. 131/3,153-63(2003)) state that: " Therefore, sPLA (2) s **may** have an important role in inflammatory allergic reactions by activating multiple mechanisms within inflammatory and immune cells, leading to production of eicosanoids, cytokines and chemokines".

Status of current clinical trials:

- Scott et al (PubMed Abstract 12783578, also cited as Expert Opin Ther.Targets, 7/3,427-40(2003)) state that:" However, progress in our understanding of the functional role of the ten secreted enzymes..phospholipid(PL) metabolism and in eicosanoid-mediated disorders, together with their emerging activity-independent and receptor-mediated functions, **is likely** to cause significant impact on current and future drug development efforts".

13. **Discussion about non-steroidal anti-inflammatory agents:**

Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications(Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of the causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

14. Specification on pages 116-118 recites various tests and assay method for binding activity of chemokine receptor. Results recited in lines 1-3 of page 118 state that:" The compounds of the Examples were found to be antagonists of the eotaxin mediated [Ca2+]I in human eosinophels and/or antagonists of the MIP-1alpha mediated [Ca2+]I in human monocytes".

. Lines 28-29 on page 118 recite:" Certain compounds of the Examples were found to be antagonists of the eotaxin mediated human eosinophil chemotaxis".

These results will only serve purpose of the preliminary screening of many compounds, and not for treating the diseases as claimed herein.

15. The facts as provided above do support the need for additional quantity of experimentation which would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the method of treatment for various disorders/conditions related to inflammation.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of instant compounds to control or prevent disorders related to inflammation

16. When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by being Inaba et al (JP10259176, also cited as Chemical Abstract DN 129:310895).

The instant claims overlap with the ref. '176 compound with a CAS RN #214846-51-2 (= 2H-1, 4-Benbzoxazine-7-carboxamide, 3,4-dihydro-3-oxo-4- (phenyl methyl)-N-[1-(phenyl methyl)-4-piperidinyl]- with the following meanings of the variables in instant Formula (I) as: X1, X2, X3, X4 and Z= -CH2- i.e. piperidine N-CH2- core;
R6= Optionally substituted phenyl-; R= 3-14 membered saturated or unsaturated ring system which consists of upto 4-ring heteroatoms independently selected from O.N.S, and the ring is optionally substituted; integers, m, n = zero; T = -CO-NH-.

19. Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Takasugi et al (WO 9313083, also cited as Chemical Abstract DN 120:30773).
The instant claims overlap with the ref. '083 compound with a CAS RN #151097-86-8 (= 1,2,4-oxadiazole-3-carboxamide, 5-(1-azabicylco [2.2.2.] oct-3-yl)-N- [1-(phenylmethyl)-

4-piperidinyl]-, dihydrochloride with the followoing meanings of the variables in instant Formula (I) as: X1, X2, X3, X4 and Z= -CH2- i.e. piperidine N-CH2- core;
R6= Optionally substituted phenyl-; R1= 3-14 membered saturated or unsaturated ring system which consists of upto 4-ring heteroatoms independently selected from O.N.S, and the ring is optionally substituted i.e. oxadiazole ring optionally substituted by azabiclo ring; integers, m, n = zero; T = -CO-NH-.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Inbana et al()JP 10259176, also cited as Chemical abstract DN 129:310895).

Inaba teaches the compounds with a core: "Substituted heterocycle-CO-NH-Pipoeridine-CH2-Phenyl"

The ref. '176 differs by having Banzoxazinone as a heterocycle with co group in 3-position. which is a heterocycle with N and O as heteroatoms and also has a 1,4-benzoxazine by other heterocycle or non-heterocycle(e.g. phenyl)CO group in 3-position.

Thus, it would have been obvious to one having ordinary skill in the art at the time of invention to prepare instant compounds by replacing a 10-membered heterobi-cycle with N and O as heteroatomsi.e. 1,4-benzoxazine by other heterocycles (monocyclic 4, 5 or 6-mbered ring(s)or non-heterocycles (e.g. phenyl) and with or without CO (= carbonyl group) in the rings so obtained.

The motivation stems from the expectation of making compounds having properties equal or better as pharmaceutical/therapeutic agents. Also, note that the ref. ' 930 teaches the utility of compounds as neovascularization inhibitors.

21. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takasugi et al (WO 9313083, also cited as Chemical abstract DN 120:30773).

Takasugi teaches the compounds with a core: " Heterocycle Substituted 1,2,4-oxadiazole-CO-NH-Pipoeridine-CH2-Phenyl"

The ref. '083 differs by having azabicylo ring instead of instant pyridine. .

Thus, it would have been obvious to one having ordinary skill in the art at the time of invention to prepare instant compounds by replacing a 6-membered azabicyclo- heterobi-cycle .pyridine or other heterocycles(monocyclic 4 , 5 or 6-mbered

ring(s)or non-heterocycles(e.g. phenyl) and with or without substituenmts as claimed herein.

The motivation stems from the expectation of making compounds having properties equal or better as pharmaceutical/therapeutic agents. Also, note that the ref. '083 teaches the utility of compounds as acetylcholinesterase inhibitors.

It has been held that a prior art disclosed compounds is sufficient to render a prima facie case of obviousness as species falling within a genus. See In re SUSI, 440 F 2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by Federal Circuit in Merck & co. V. Biocraft Laboratories, 847 F 2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir.1989).See In re Dillon 16 USPQ 2nd. 1897, 1923 regarding a prima facie case of obviousness of structurally similar compounds disclosed by prior art" regardless lo the properties disclosed in the inventor's application.

All this is especially considered so in the absence of timely, verified, comparative data, commensurate in scope to the claims sought, clearly and convincingly proving obvious ness over the art(s) as applied above. If applicants intend to rely on unusual or unforseen results demonstrate patentability, attention is drawn to MPEP 716. It is also pointed out that arguments of patentability to differences either not in, or not made clear by, claim language will be of no avail as it is the claims, per se, that are the measure of the invention.

Conclusion

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is 703 308 4709. The examiner can normally be reached on 6:30 to 5:00 pm.' Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on 703 308 4716 or Sr. Examiner Mr. Richard Raymond at 703 308 4523.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.

Sudhaker B.Patel, D.Sc.Tech.
October 20, 2003.

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